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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/720,469	12/22/2000	Kyogo Itoh	0020-4792P	2449

2292 7590 10/28/2004

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EXAMINER	
YU, MISOOK	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 10/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/720,469	ITOH ET AL.	
	Examiner	Art Unit	
	MISOOK YU, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,4,8,10 and 12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,4,8,10 and 12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 09/13/2003 has been entered.

Claims 2, 4, 8, 10, and 12 are pending and examined on merits. The search has been extended to other species.

This Office action contains new grounds of rejection.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 102, Withdrawn

The rejection of the claims under 35 U.S.C. 102(b) as being anticipated by Price et al (1991, Proc. Natl. Sci. USA, vol. 88, pages 1903-1907) is withdrawn in view of the amendment.

The Following Are New Grounds of Rejection

Claim Rejections - 35 USC § 112

Claims 2, 4, 8,10, and 12 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for SEQ ID NOs: 1, 2, 39-43 in combination of one specific HLA, i.e. HAL-A24, does not reasonably provide enablement for any other 8-14 amino acids in length, which is a fragment of cyclophilin B sequence of SEQ ID

NO:44 with any other HLA molecule. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Claim 2 is drawn to an isolated tumor antigen peptide of 8-14 amino acids in length, which is a fragment of which is a fragment of cyclophilin B sequence of SEQ ID NO:44, and that binds to an HLA antigen and is recognized by cytotoxic T lymphocytes. Claim 4 is drawn to SEQ ID NOs 1-36, and 41-43, and claim 8 is drawn to isolated antigen peptides, in which position 2 in SEQ ID NOs:1-11 is substituted by the recited amino acids. Claims 10 is drawn to SEQ ID NOs :37-40, and claim 12 is drawn to composition comprising the peptide of claims 2, 4, 8, 10 as the main ingredient.

Riott et al (Immunology, Fourth Edition, 1996, Mosby, page 7.9-7.11) teach that a foreign protein is entered in a host due to infection or other event such as cancer development in a host, it is broken down into short chains of amino acids known as peptides. The cell then "presents" these cleaved peptides on its surface via a protein known as MHC, which stands for major histocompatibility complex. In this manner, the

cell "marks" itself to be destroyed. Special immune system cells known as cytotoxic T lymphocytes (CTLs) then recognize and destroy the marked cells. CTLs are antigen-specific; that is, the introduction of a particular antigen into the body activates specialized CTLs that recognize that antigen. The CTLs then target those cells whose surfaces are marked with a fragment of the activating antigen. T cells recognizes cell-bound antigen in association with MHC molecules. MHC class I and class II act as guidance systems for T cells. This is known as MHC restriction. Only a minority of peptide fragments from a protein antigen is able to bind particular MHC molecules. Different MHC molecules bind different sets of peptides. Riott et al specifically teach Fig. 7.22 and Fig. 7.23, and also page 7.10, right column that the peptides sizes 12-15 are optimal for MHC molecule class I and certain amino acids at certain positions are critical for binding to MHC class I.

The specification at pages 43-60 discloses that SEQ ID NOs: 1, 2, 39-43 can be used in combination of one specific HAL-A24 but the specification does teach which other fragments or derived peptides claimed in the instant claims can be used to as a tumor antigen capable of stimulating immune response and binds to one or more MHC molecules presented on the surface of cells, elicit a cytolytic response. It is not clear if (CTLs) could be generated using numerous claimed fragments.

The specification does not disclose common structural attributes that stimulate an immune response and binds to one or more MHC molecules presented on the surface of cells. There is insufficient guidance regarding the parameters and sequence of peptides which correlate with the ability to stimulate T cell with any MHC molecule

and generate CTLs with claimed specifity/activity. There is insufficient guidance regarding selection of peptides that meet the instant criteria of stimulating T lymphocytes with specific activity. Thus, there is insufficient guidance regarding the parameters and sequences of peptides which correlate with the ability to be recognized by the specific CTL clone.

US Pat. 5,840,839 (Nov. 24, 1998) teach at column 19 that finding a peptide that binds to a MHC molecules and stimulates immune response is not a trivial matter. The '839 patent at column 19, lines 53 to 67 teaches that structure a T cell epitope that stimulates immune response in context of MHC molecules is unpredictable in the current state of art. The '839 patent at columns 19-20, and Table 1 teaches that the various candidate T cell epitopes selected based on theoretical binding motif of one class of MHC molecule, i.e. HLA-A31 do not work when they are experimentally tested as shown in Table 1. This suggests that theoretically selected T cell binding motifs have to be tested experimentally in order to determine whether they are actually T cell epitopes or not.

The specification provides insufficient guidance with regard to theses issues and provides no working examples of a peptide that would work with any MHC molecule. Considering the state of art, the broad scope of claims in respect to the nature of peptide and also to the nature of MHC molecules, it is concluded that that undue experimentation is required to practice the claimed invention. It is noted that law requires that the disclosure of an application shall inform those skilled in the art how to make the alleged discovery, not how to screen it for themselves.

Searching potential T-cell epitopes in cyclophilin B using existing software (this use is considered as research, not patentable use) does not require undue experimentation. Undue experimentation is required to use the potential T-cell epitopes as immunogen to illicit anti-tumor response i.e. using as an tumor antigen peptide in a subject. The specification fails to teach how administration of the claimed peptide would produce a sufficient amount of CTLs, to destroy tumor cells expressing cyclophilin B. Cancer therapy using immunogen is still unpredictable in the art. The specification teaches that SEQ ID NO:44 is a self antigen, rather than a mutated antigen, as it is expressed on normal tissues as well as cancerous tissues and that self-tolerance may eliminate T cells that are capable of recognizing these epitopes with high avidity (Sherman, LA et al, 1998, Critical reviews in Immunol, 18(1-2): 47-54, see especially at the abstract and Table 2). In other words, only CTLs with low affinity are left, which may not be optimal for tumor elimination *in vivo*. One of the problem is that after some period of time in the presence of tumor cells, T cells may lose their functional activity. Lauritzsen et al (International Journal of Cancer, 1998, Vol. 78, pp. 216-222) teach that a clonal deletion of thymocytes is a major event in T-cell tolerance which could lead to a tumor escape mechanism. In transgenic mice homozygous for HLA-specific CD+4 T-cells which are specific for a MOPC315 plasmacytoma, injection of a large number of tumor cells results in apoptosis of immature and mature transgenic CD+4+8 and CD+4 thymocytes. This negative selection was specific for the transgenic thymocytes that would complement the idiotype of the immunoglobulins of the MOPC315 plasmacytoma, because injection of tumor cells from a plasmacytoma which had a

different idiotype of immunoglobulins failed to elicit the clonal deletion. Lauritzsen et al teach that injection of purified MOPC315 protein, versus the tumor cells, caused a profound reduction of the specific thymocytes specific to the idiotype of the plasmacytoma. Lauritzsen et al conclude that deletion of tumor specific thymocytes may represent a major escape mechanism in patients with cancers that secrete of shed antigens. In the instant case, the antigens are known self-antigens. It would be reasonable to conclude that said normal antigens are presented within the thymus to developing thymocytes and T-cells with high affinity for said antigens are deleted as "self". It would be also reasonable to conclude that administration of the claimed polypeptides or cells expressing said polypeptides would not result in an efficacious vaccine as a T-cell response would not be evoked due to the process of clonal deletion in the thymus, rendering the host devoid of T-cells which are specific to the self-protein. Sarma et al (Journal of Experimental Medicine, 1999, Vol. 189, pp. 811-820) states that a critical issue in therapeutic regiments comprising the administration of tumor antigens for immunotherapy is whether unmutated tumor antigens which are expressed in normal cells impose special restrictions on the CTL response in vivo. Using transgenic mice wherein the antigen specific T cells specific for the P1A non-mutated tumor antigen are expressed at high levels and remain responsive to the P1A antigen when assayed in vitro, it was found that P1A antigen expressed in the thymus resulted in clonal deletion of said specific T-cells Sarma et al note that although said transgenic mice produce an overwhelming majority of T cells that are specific for P1A, said mice are no more resistant to cells expressing P1A than non-transgenic litter mates. Sarma et al

concludes that even thought P1A can be a tumor rejection antigen, the effector function of P1A specific CTL is restrained in vivo and that these results have important implications for the strategy of tumor immunotherapy. With regard to the isolation of two T-cells which are specific for the instant antigen presented in the context of HLA-A24, it cannot be determined if this is a reliable indicator that in all patients, with any of the types of cancers listed on page 20, would have a T-cell available after thymic selection which would react with said antigen in the context of HLA-A24 or any other MHC molecule.

The specification does not provided any evidence that any of the vast number of possible potential cyclophilin B derived T-cell epitopes might be able to be used for cancer therapy. The specification does not disclose or suggest any other use of the claimed peptides other than as a tumor antigen.

It is concluded based on the references discussed above, that the state of the art with respect to treating cancer patients of administering tumor antigens is unpredictable. The specification does not provide any disclosure that the administration of the claimed polypeptides would generate CTLs which lyse the cells of a tumor and it cannot be predicted based on disclosure of the specification. Considering the limited guidance, no working examples in the specification, and the unpredictability in the art, it is concluded that undue experimentation is required to use the full scope of the claimed invention.

It is noted that law requires that the disclosure of an application shall inform those skilled in the art how to make the alleged discovery, not how to screen it for themselves.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MISOOK YU, Ph.D. whose telephone number is 571-272-0839. The examiner can normally be reached on 8 A.M. to 5:30 P.M., every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey C Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Misook Yu

MISOOK YU, Ph.D.
Examiner
Art Unit 1642